Risk varies inversely with knowledge.

Irving Fisher, The Theory of Interest, 1930

Forum

Cell Signaling

Thousands of organic compounds are currently synthesized and released into the environment, often with only a minimum of regulation and no clear understanding of how chemicals interact with biological systems. The science of environmental medicine is now acting fast to respond to the need for such information by developing approaches to investigate these interactions.

Biologists are using advanced genetic and molecular tools, for example, to define the pathway by which an individual cell is poisoned. This new area of investigation, known as cell signaling, traces the interplay of proteins within a cell from the instant the cell is stimulated from outside, via its ion channels or membrane receptors, to the moment and method of its destruction. Cell signaling is seen as the key to understanding how basic cellular processes go awry in a variety of dysfunctions, including cancer.

Neurotoxicologists are now using the principles of cell signaling formulated by neurobiologists to study the fundamentals of environmental poisoning. For example, scientists are just now understanding what happened in cases of pesticide poisoning long assigned to the history books. One such event was the "Ginger–Jake" case, in which about 20,000 Americans were paralyzed in the 1920s from eating an extract of ginger called "Jamaica Ginger" that had been treated with an organophosphorus ester.

This ester belongs to a class of pesticides that produce a syndrome known as organophosphorus ester-induced delayed neurotoxicity (OPIDN), manifested by paresis in the legs, hands, and thighs that occurs days to weeks after exposure. In the later stages of OPIDN, symptoms of spinal cord injury such as spasticity and ataxia become evident.

Investigators now know that the crucial biochemical journey these organophosphides take starts at the cell's calcium channel, the protective gateway that limits entry of calcium into the cell. Calcium is involved in the regulation of a variety of nerve functions and is the ultimate target for many toxins; the death of a cell is often associated with the cell's inability to exclude calcium. Some toxins can also act by perturbing calcium signaling to the point that cell growth is inappropriately favored.

The pesticide in the Ginger–Jake case directly affects a second messenger in the signaling pathway known as calmodulin protein kinase II, an enzymatic catalyst that phosphorylates a number of cytoskeletal proteins. A recent experimental injection of an organophosphide in chickens resulted in such increased phosphorylation that the nerve cells' neurotubules and neurofilaments broke down and bound together. The result surprised researchers: they found a jumble of nerve tangles of the type seen in such degenerative diseases as Alzheimer's disease.

Research on cell signaling holds promise of unraveling the cellular basis of a wide variety of neurodegenerative dysfunctions and other adverse health effects that may be related to chemical exposure.

Volunteer Duty

Continuing a 36-year tradition, the Student Conservation Association (SCA) sent some 1500 high school, college, and older individuals streaming into 308 federal and state park sites nationwide last summer to learn about resource management through hands-on conservation projects.

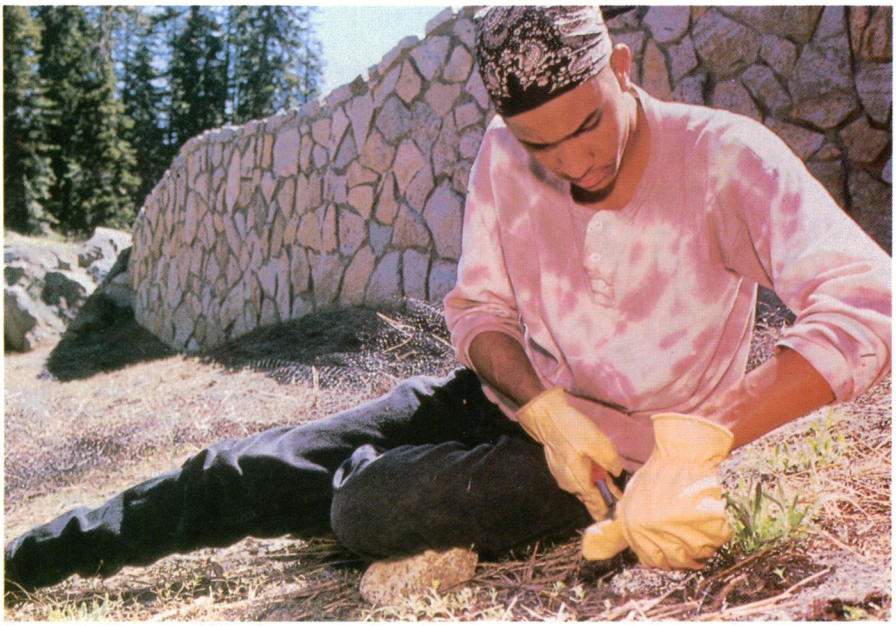
More than 450 high school students worked on projects ranging from restoring damaged areas of Clearwater National Forest in Idaho to maintaining and repairing trails in Rocky Mountain National Park, Colorado. Approximately 1100 resource assistants, 18 years or older, worked as professional aides with SCA's cooperating agencies on projects including backcountry patrols in the Denali National Park and Preserve, Alaska, interpreting historical sites such as Fredericksburg and Spotsville National Military Park, Virginia, and monitoring wildlife and erosion control at Baxter State Park, Maine. Volunteers logged about 700,000 hours of volunteer time in the nation's parks this past season. In addition, the SCA also supported two international volunteer programs between the United States, Mexico, and Canada.

The SCA was begun in 1957 from the idea that public lands offer a superb training ground for individuals in conservation techniques of soil, water, vegetation, and wildlife. The SCA works closely with federal agency partners: the National Park Service, the U.S. Forest Service, the Bureau of Land Management, and the U.S. Fish

Lesley Schuler

Avian answers. Volunteers at Mattamuskeet National Wildlife Refuge in North Carolina study effects of mercury contamination on ospreys.

John Goubeaux



Regreening Yosemite. SCA's Conservation Career Development program includes projects like revegetation of parks.

and Wildlife Service, among others. Foundations, corporations, and other supporting organizations provide additional funding.

In addition to the high school and resource assistant programs, SCA sponsors a program dedicated to bringing cultural diversity to the conservation workforce. The Conservation Career Development Program (CCDP), funded by a grant from the National Fish and Wildlife Foundation, seeks to broaden the conservation arena by involving people within the context of their own cultures. According to Cameron Bayne, a CCDP High School Component Supervisor, "Our environment is diverse, and those who care for it should be as diverse."

Butadiene and Styrene Risks

Workers in plants that manufacture synthetic rubber and reinforced plastics are being exposed to levels of butadiene and styrene gases thousands of times greater than the general population, possibly correlating to greater risk of cancers and other occupational health hazards.

Such was the evidence presented at an international symposium on "Health Hazards of Butadiene and Styrene" held in Finland in April. More than 160 scientists from 17 countries attended the symposium, organized by the Finnish Institute of Occupational Health and the International Agency for Research on Cancer.

The United States currently produces approximately 3 billion pounds a year of butadiene, mainly for the production of synthetic rubber, and 9 billion pounds a year of styrene, used in plastics and products such as Styrofoam. Though the general population may be exposed to these gases in the air, cigarette smoke, water, or foods, the major concern of the symposium was for workers in these industries whose exposures far exceed environmental levels.

Current occupational exposure to butadiene in the United States is generally less than 10 parts per million (ppm), with measured excursions as high as 374 ppm, compared to urban air concentrations of 1–10 parts per billion (ppb). Although OSHA has proposed lowering the permissible occupational exposure level to 2 ppm, this proposal has not been implemented, and the level remains at 1000 ppm. Cancer risk estimates for workers exposed to the proposed 2 ppm standard range from 0.2 per 10,000 workers to 600 per 10,000 workers, depending on the type of tumor.

Average exposures to styrene in polystyrene manufacturing plants are less than 5 ppm. In the reinforced plastics industry, average concentrations are 45 ppm, though peak concentrations may reach hundreds of parts per million.

Health risks to animals and humans from exposure to butadiene and styrene, including genetic damage and cancer, were presented at the symposium. Epoxide intermediates of butadiene were shown to cause gene mutations at both the *hprt* and *tk* loci in human lymphoblastoid cells and at the *hprt* locus in mouse splenic lymphocytes. Increases in chromosomal damage in human lymphocytes were reported in a number of studies of workers exposed to styrene; however, the dose–response relationships are not clear.

Lung tumors have been induced in mice at the lowest concentration of butadiene (6.25 ppm) ever used in a long-term study. Gene mutations in the p53 tumor-suppressor gene, analogous to those found in a wide variety of human cancers, were characterized in both lung and mammary gland tumors in mice. Although no adequate inhalation studies have been reported for styrene, gavage exposure to styrene oxide, a metabolite of styrene biotransformation, caused forestomach tumors in rats and mice.

Epidemiology studies reveal associations between occupational exposure to butadiene and deaths due to leukemias. A case–control study of leukemias in plants that manufacture styrene and butadiene rubber showed a seven- to ninefold increase in risk for workers exposed to butadiene, although some believe the risk is actually much lower or nonexistent. Though no such association was shown for styrene, small increased risks of leukemias and lymphomas were reported in workers exposed to styrene in the reinforced plastics industry.

Development of physiologically based pharmacokinetic models of the uptake, tissue distribution, and metabolism of styrene and butadiene in the rat, mouse, and human was presented at the symposium. Differences in internal doses of mutagenic epoxides in rats and mice are too small to account for the different carcinogenic effects of butadiene in these species. Discussions also highlighted the need for more information on metabolism of these chemicals in organs other than the liver and lung. There appear to be two groups among the human population with different levels of sensitivity to the genotoxic effects of these chemicals. More research is needed on the metabolic variability of humans, particularly in susceptible populations. New markers of exposure for butadiene and styrene were also presented at the conference, which scientists hope may be useful for human biomonitoring and provide some of the much needed information to evaluate human risks from exposure to these two chemicals.

Kids at Risk

Children may be at increased risk for effects of pesticides, a National Academy of Sciences report concluded in July. The report cited deficiencies in the way the government calculates safe levels of pesticides on foods and its regulation of pesticides.

The NAS report, *Pesticides in the Diets of Infants and Children*, states that children might be highly sensitive to pesticides on food and that they consume 60 times more fruit than adults, leading to higher doses of pesticides. "Older infants and young children may metabolize pesticides more exten-